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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,411	11/10/2005	Clifford Charles Shone	1581.0130005/TJS/JJY	7312

26111 7590 08/31/2009

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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
08/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,411	SHONE ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/15/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 15, 2009 has been entered.

Amendment Entry

2. The amendment filed June 15, 2009 has been entered. Claims 1 has been amended. Claims 1-30 are pending and under examination. Claims 31-41 are cancelled.

Information Disclosure Statement

3. The information disclosure statements filed on 6/15/2009 has been considered. An Initialed copy is enclosed.

Rejections Withdrawn

4. In view of the Applicant's amendment and remark the following rejections are withdrawn.

a) Claims 1-30 rejected under 35 U.S.C. 101 because the claimed invention was directed to non-statutory subject matter wherein said recitation of a polypeptide did not indicate the hand of man because the polypeptide can naturally occur and was deemed products of nature is withdrawn in light of applicants amendment.

Claim Rejections Maintained - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. The rejections of claim 1-30 under 35 U.S.C. 102(b) as being anticipated by Binz et al 1990 Eur. J. Biochem. 189:73-8 is maintained for the reasons set forth in the previous office action.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 102(b), June 15, 2009 is carefully considered, but not found to be persuasive for the reasons below.

Applicants argue the amended claims are not anticipated by Binz et al. because the sequence recited in Binz et al. is full length BoNT/A holotoxin which comprises a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc. Therefore Applicants respectfully submit that the rejection under 35 U.S.C. 102 has been obviated, and should be withdrawn.

Examiner's Response to Applicant's Arguments:

In response to applicant's statement as set forth supra, Binz et al discloses the amino acid sequence as set forth in claimed SEQ ID NO: 66. The claims do not recite any closed claim language such that additional amino acids must be excluded. Moreover, the limitations of the claim allow for the full length molecule, because the claim is drawn to a fragment or variant thereof, i.e., the full length molecule is a "variant" of the claimed molecule which lacks a functional C-terminal. Therefore limitations have been met.

New Grounds of Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14, 16-32, 34, 37-39, and 54 of copending US Application No. 11/644,010.

A) In the instant case, the claims are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein:- said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence (I) SEQ ID NO: 66; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (claim 1), wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (claim 4), wherein said second domain is a clostridial toxin heavy chain Hc portion (claim 5), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (claim 6), wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain (claim 7), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (claim 8), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain (claim 9), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (claim 10), wherein the second domain

comprises the 422 N-terminal amino acids of tetanus heavy chain (claim 11), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (claim 12), comprising a site for cleavage by a proteolytic enzyme (claim 13), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 14), wherein the cleavage site allows proteolytic cleavage of the first and second domains (claim 15), wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein than does the-polypeptide prior to said proteolytic cleavage (claim 16), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (claim 17), wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc (claim 18), further comprising a third domain that binds the polypeptide to a cell, by binding of the third domain directly to a cell or by binding of the third domain to a ligand or to ligands that bind to a cell (claim 19), wherein said third domain is for binding the polypeptide to an immunoglobulin (claim 20), wherein said third domain is a tandem repeat synthetic IgG binding domain derived from domain b of Staphylococcal protein (claim 21), wherein said third domain comprises an amino acid sequence that binds to a cell surface receptor (claim 22), wherein said third domain is insulin-like growth factor- 1 (IGF- 1) (claim 23), including a spacer molecule between the first and second domains (claim 24), including a spacer molecule between the second and third domains (claim 25), further comprising a purification tag that binds to an affinity matrix thereby facilitating purification of the polypeptide using said matrix (claim 26), including a spacer molecule between the purification tag and the polypeptide (claim 27), wherein said purification tag binds to an affinity matrix of glutathione sepharose (claim 28), wherein a first protease cleavage site is incorporated between said single chain polypeptide and the purification tag, said protease cleavage site enabling proteolytic separation of said polypeptide from said purification tag (claim 29).

B) Claims 1-14, 16-32, 34, 37-39, and 54 of U.S. Application 11,644,010 teach a single chain polypeptide comprising first and second domains, wherein:-said first domain is a clostridial neurotoxin light chain (such as botulinum neurotoxin light chain, tetanus neurotoxin light chain (see claims 2-3)) or a fragment or a variant thereof, wherein said first domain is

capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 1).

US Application No. 11/644,010 teach a second domain that lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds, wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain, a tetanus neurotoxin heavy chain, wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (see claim 6), wherein said second domain is a clostridial toxin heavy chain HN portion (see claim 7), wherein the second domain lacks a C- terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 8), further comprising a third domain that binds the polypeptide to a cell, by binding of the third domain directly to a cell or by binding of the third domain to a ligand or to ligands that bind to a cell (see claim 9), wherein said third domain is for binding the polypeptide to an immunoglobulin (see claim 10), wherein said third domain is a tandem repeat synthetic IgG binding domain derived from domain b of Staphylococcal protein A (see claim 11), wherein said third domain comprises an amino acid sequence that binds to a cell surface receptor (see claim 12), wherein said third domain is insulin-like growth factor-1 (IGF-1) (see claim 13), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (see claim 14), wherein the

second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain (see claim 16), wherein clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (see claim 17), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain (see claim 18), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (see claim 19), wherein the clostridial neurotoxin light chain is a botulinum toxin type B light chain, and the second domain comprises the 417 N-terminal amino acids of a botulinum toxin type B heavy chain (see claim 20), wherein one clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a tetanus toxin chain (see claim 21), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (see claim 22), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (see claim 23), wherein a polypeptide is lacking a portion designated Hc of a clostridial neurotoxin heavy chain (see claims 24-25), comprising a site for cleavage by a proteolytic enzyme (see claim 26), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 27), wherein the site for cleavage allows proteolytic cleavage of the first and second domains (claim 28), wherein the site for cleavage allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein than does the polypeptide prior to said proteolytic cleavage (see claim 29), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (see claim 30).

US Application No. 11/644,010 teach a fusion protein comprising a fusion of (a) a polypeptide with (b) a purification tag that binds to an affinity matrix thereby facilitating purification of the fusion protein using said matrix (see claim 31), wherein said purification tag binds to an affinity matrix of glutathione sepharose (see claim 32), wherein a first protease cleavage site is incorporated between the polypeptide and purification tag, said protease cleavage site enabling proteolytic separation of the polypeptide from the purification tag (see claim 34), including a spacer molecule between the first and second domains and second and third domains (see claims 37-38), including a spacer molecule between the purification tag and the polypeptide (see claim 39); a single chain polypeptide of: SEQ ID NO: 66 (see claim 54 and stic results).

Although the conflicting claims are not identical, they are not patentably distinct. The U.S. Application 11,644,010 recites the "single chain polypeptide". The species of the single chain polypeptide anticipate the genus claims of any "single chain polypeptide".

Thus, claims 1-29 encompassing "single chain polypeptide" in the present application is obvious over claims 1-14, 16-32, 34, 37-39, and 54 of U.S. Application 11,644,010.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1-3, 5-15, and 17-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 11-23, 25-26 of copending US Application No. 11/077,550.

A) In the instant case, the claims are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein:- said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence (I) SEQ ID NO: 66; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (claim 1), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain

and tetanus neurotoxin heavy chain (claims 2-3), wherein said second domain is a clostridial toxin heavy chain Hc portion (claim 5), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (claim 6), wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain (claim 7), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (claim 8), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain (claim 9), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (claim 10), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (claim 11), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (claim 12), comprising a site for cleavage by a proteolytic enzyme (claim 13), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 14), wherein the cleavage site allows proteolytic cleavage of the first and second domains (claim 15), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (claim 17), wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc (claim 18).

B) Claims 1-9, 11-23, 25-26 of US Application No. 11/077,550 teach an antigenic composition comprising a single chain polypeptide comprising first and second domains, wherein: said first domain is a clostridial neurotoxin light chain or a variant thereof, or a fragment of said light chain or variant wherein said variant or fragment has a common antigenic cross reactivity to said clostridial neurotoxin light chain; and said second domain is a clostridial neurotoxin heavy chain HN portion or a variant, wherein said variant or fragment has a common antigenic cross reactivity to said clostridial neurotoxin heavy HN portion; and wherein said domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, and wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the

natural cell surface receptors to which native clostridial neurotoxin binds (second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds) (see claim 1), wherein said clostridial neurotoxin light chain is a botulinum light chain/tetanus neurotoxin light chain (see claims 2-3), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin heavy chain and tetanus neurotoxin heavy chain (see claims 4-5), wherein said second domain is a clostridial toxin heavy chain HN portion (see claim 7), wherein the second domain lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 8), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A/type B chain (see claims 9 and 12),wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain (see claim 11), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain (see claim 13), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (see claim 14), wherein the clostridial neurotoxin light chain is a botulinum toxin type B light chain, and the second domain comprises the 417 N-terminal amino acids of a botulinum toxin type B heavy chain (claim 15), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a tetanus toxin chain (claim 16), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (see claim 17), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (see claim 18), wherein a polypeptide is lacking a portion designated Hc of a clostridial neurotoxin heavy chain (see claims 19-20), comprising a site for cleavage by a proteolytic enzyme (see claim 21), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 22), wherein the site for cleavage allows proteolytic cleavage of the first and second domains (claim 23), antigenic composition obtainable by a first nucleic acid sequence encoding said cleavage site within a second nucleic acid encoding a single chain polypeptide (see claim 25), wherein a single chain polypeptide (antigenic comprising a single chain polypeptide) is SEQ ID: 66 (see claim 26 and STIC results attachment).

Although the conflicting claims are not identical, they are not patentably distinct. The U.S. Application 11,077,550 recites the "single chain polypeptide". The species of the "single chain polypeptide" anticipate the genus claims of any "single chain polypeptide".

Thus, claims 1-3, 5-15, and 17-18 encompassing the "the isolated polypeptide" in the present application are obvious over claims 1-9, 11-23, 25-26 of U.S. Application 11,077,550.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-18, and 24, 26-30 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10-17, 20-29, 31, and 39-42 of US Patent No. 7,192596.

A) In the instant case, the claims 1-18 and 24, 26-30 of in the instant application are drawn to an isolated polypeptide, wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein:- said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence (I) SEQ ID NO: 66; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (claim 1), wherein said clostridial

toxin heavy chain is a botulinum neurotoxin heavy chain (claim 2), wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain (claim 3), wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (claim 4), wherein said second domain is a clostridial toxin heavy chain HN portion (claim 5), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (claim 6), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (claim 8), wherein the second domain comprises the 107 N-terminal or 423 N-terminal amino acids of a botulinum toxin type A and B heavy chains (claims 7 and 9), wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain (claim 10), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (claim 11), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (claim 12), comprising a site for cleavage by a proteolytic enzyme (claim 13), wherein the cleavage site is not present in a native clostridial neurotoxin (claim 14), wherein the cleavage site allows proteolytic cleavage of the first and second domains (claim 15), wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein that does the polypeptide prior to said proteolytic cleavage (claim 16), a polypeptide obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide (claim 17), wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated Hc (claim 18), inclusing a spacer molecule between the first and second domains (claim 24), comprising a site for cleavage by a proteolytic enzyme (see claim 26), including a spacer molecule between the purification tag and the polypeptide (claim 27), wherein said purification tag binds to an affinity matrix of glutathione sepharose (claim 28), wherein first protease cleavage site is incorporated between said single chain polypeptide and the purification tag said protease cleavage site enabling proteolytic separation of said polypeptide from said purification tag (claim 29), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (claim 30).

B) Claims 1-8, 10-17, 20-29, 31, and 39-42 of US Patent No. 7,192596 teach a single chain polypeptide consisting essentially of first and second domains, wherein: said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof wherein said second domain (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein the second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated HC thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 1), wherein said clostridial neurotoxin light chain is a botulinum neurotoxin light chain (see claim 2), wherein said clostridial neurotoxin light chain is a tetanus neurotoxin light chain (see claim 3), wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin heavy chain (see claim 4), wherein said clostridial neurotoxin heavy chain is a tetanus neurotoxin heavy chain (see claim 5), wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin (see claim 6), wherein said second domain is a clostridial neurotoxin heavy chain HN portion (see claim 7), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain (see claim 8), wherein the second domain comprises the 423 N-terminal amino acids of botulinum neurotoxin type A heavy chain (see claim 10), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain (see claim 11), wherein the second domain comprises the 107 N-terminal amino acids of a botulinum neurotoxin type B heavy chain (see claim 12), wherein the second domain comprises the 417 N-terminal amino acids of botulinum neurotoxin type B heavy chain (see claim 13), wherein the clostridial neurotoxin light chain is a botulinum neurotoxin type B light chain, and the second domain comprises the 417 N-terminal amino acids of a botulinum neurotoxin type B heavy chain (see claim 14), wherein one or both of said clostridial neurotoxin light chain and said clostridial neurotoxin heavy chain is a tetanus toxin chain (see

claim 15), wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain (see claim 16), wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain (see claim 17), comprising a site for cleavage by a proteolytic enzyme, wherein said cleavage site is located between said first domain and said second domain (see claim 20), wherein the cleavage site is not present in a native clostridial neurotoxin (see claim 21), wherein the site for cleavage allows proteolytic cleavage of the first and second domains (see claim 22), wherein the site for cleavage allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein than does the polypeptide prior to said proteolytic cleavage (see claim 23).

US Patent No. 7,192596 teach a polypeptide produced by a process comprising (a) inserting a first nucleic acid sequence encoding said cleavage site into a second nucleic acid sequence encoding the polypeptide, and (b) expressing said first and second nucleic acid sequences to obtain said polypeptide (see claim 24); a fusion protein consisting essentially of a fusion of (a) a single chain polypeptide consisting essentially of first and second domains and (b) a purification tag that binds to an affinity matrix thereby facilitating purification of the fusion protein using said matrix (see also claim 41); wherein said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein the second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated HC thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 25), wherein said purification tag binds to an affinity matrix of glutathione sepharose (see claim 26), wherein a first protease cleavage site is incorporated between the polypeptide and purification tag said first protease cleavage site enabling proteolytic separation of the polypeptide from the purification tag (see

claim 27), including a spacer molecule between the purification tag and the polypeptide (see claim 29); a single chain polypeptide consisting of first and second domains, wherein: said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain cleaves one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain (i) translocates the polypeptide into a cell or (ii) increases the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocates the polypeptide into a cell and increases the solubility of the polypeptide compared to the solubility of the first domain on its own; and wherein the second domain lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated HC thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds (see claim 31), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (see claims 39-40), further comprising a spacer molecule between the first and second domains (see claims 28 and 42), wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein that does the polypeptide prior to said proteolytic cleavage (see claim 23), wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains (see claim 25).

Although the conflicting claims are not identical, they are not patentably distinct. The U.S. Patent No. 7,192596 recites the "single chain polypeptide". The species of the "single chain polypeptide" anticipate the genus claims of any "single chain polypeptide".

Thus, claims 1-18, and 24-30 encompassing the "the isolated polypeptide" in the present application are obvious over claims 1-8, 10-17, 20-29, 31, and 39-42 of US Patent No. 7,192596.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Grounds of Objections

9. Claim 18 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 18 is drawn a polypeptide, wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated $H_{c\ and}$ dependent from claim 1. Claim 18 does not further limit the single chain polypeptide in claim 1.

10. The disclosure is objected to because of the following informalities: p. 3, Kozaki et al citation is incomplete. Applicants should insure that all references cited in specification are proper. Appropriate correction is required.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The independent claim 1 and all dependent claims 2-30 are drawn to an isolated

polypeptide, wherein said isolated polypeptide is a single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein:- said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence (I) SEQ ID NO: 66; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of a single chain polypeptide, Applicant must adequately describe both domains of clostridial neurotoxin light chain and SEQ ID NO: 66 fragment/variant forms that are capable of cleaving vesicle or plasma membranes. Applicants must also describe the domain of clostridial neurotoxin heavy chain fragment/variant forms that are capable of translocating the polypeptide in the cell and increasing the solubility of the polypeptide.

The specification states, "a variant is an L-chain (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial L-chain sequence" (see pg. 4 last paragraph). The specification further states in one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial L-chain sequence (see p. 4; see also pp. 12-13). However, any such fragment or variant must retain the aforementioned cleavage function." (see p. 4; see also pp. 12-13). The specification states, "a variant is an HN portion (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial HN domain sequence. In one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial HN sequence. However, any such fragment or variant must retain the aforementioned (i) translocation and/or (ii) improved solubility function." (pp. 6-7; see also p. 13).

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of a single chain polypeptide, to which the claims are drawn, such as a correlation between the structure of an isolated single chain polypeptide structure comprising fragments or variants of the domains, and its functions, the capability of cleaving vesicle or plasma membranes (clostridial neurotoxin light chain and SEQ ID NO: 66) and also translocating the polypeptide in the cell and increasing the solubility of the polypeptide (clostridial neurotoxin heavy chain), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus aforementioned above. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the amino acid or which amino acids might be replaced so that the resultant amino acid retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant amino acid retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus aforementioned above to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of a single chain polypeptide comprising fragments or variants of the domains capability of cleaving

vesicle or plasma membranes (clostridial neurotoxin light chain and SEQ ID NO: 66) and also translocating the polypeptide in the cell and increasing the solubility of the polypeptide (clostridial neurotoxin heavy chain).

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant/fragment species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has

Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of an isolated single chain polypeptide of the domains of fragments or variants comprising clostridial neurotoxin light chain, SEQ ID NO: 66, and clostridial neurotoxin heavy chain, the skilled artisan could not immediately recognize or distinguish members of the claimed genus aforementioned above capability of cleaving vesicle or plasma membranes (clostridial neurotoxin light chain and SEQ ID NO: 66) and also translocating the polypeptide in the cell and increasing the solubility of the polypeptide (clostridial neurotoxin heavy chain). Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of fragments/variants in the single chain polypeptide claimed invention capable of cleaving vesicle or plasma membranes (clostridial neurotoxin light chain and SEQ ID NO: 66) and also

translocating the polypeptide in the cell and increasing the solubility of the polypeptide (clostridial neurotoxin heavy chain) is not deemed representative of the genus of an isolated single chain polypeptide of the domains of fragments or variants comprising clostridial neurotoxin light chain, SEQ ID NO: 66, and clostridial neurotoxin heavy chain to which the claims refer and therefore the claimed invention is not properly disclosed.

Claim Rejections - 35 USC § 112

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single chain polypeptide (first and second domain is clostridial neurotoxin light chain and clostridial neurotoxin heavy chain respectively), wherein single chain polypeptide comprising SEQ ID NO:66, does not reasonably provide enablement for a single chain polypeptide comprising fragments or variants thereof of the Clostridial neurotoxin light chain or Clostridial neurotoxin heavy chain or SEQ ID NO:66. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is not enabled for any single chain polypeptide comprising fragments or variants thereof of the domains comprising clostridial neurotoxin light and heavy chains or the fragment or variants of SEQ ID NO: 66. Furthermore, the specification does not reasonably enable any single chain polypeptide comprising fragments or variants thereof of the domains and SEQ ID NO: 66 aforementioned above for cleavage (first domain), translocation into a cell, and/or increasing the solubility (second domain). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention:

The instant claims are drawn to an isolated polypeptide, wherein polypeptide is a single chain polypeptide comprising first and second domains, and wherein: said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain HN portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence (I) SEQ ID NO: 66; or (II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

Breadth of the claims

The breadth of the claims is very broad and the quantity of experimentation required is undue. The claims encompass all fragments and variants of clostridial neurotoxin light chain, clostridial neurotoxin heavy chain portion or a fragment, and further fragments and variants of SEQ ID NO: 66 which are overly broad. The claims encompass a myriad of possible combinations that would comprise the single chain polypeptide as claimed. Furthermore the claims encompass any type of modifications (substitution, insertion, deletion, etc.) and the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Guidance in the specification/Working Examples

The specification states, "a variant is an L-chain (or fragment thereof) in which one or more amino acid residues has been altered vis-a-vis a native clostridial L-chain sequence" (see pg. 4 last paragraph). The specification further states in one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial L-chain sequence (see p. 4; see also pp. 12-13). However, any such fragment or variant must retain the aforementioned "cleavage" (see p. 4; see also pp. 12-13). The specification states, "a variant is an HN portion (or fragment thereof) in which one or more amino acid residues has been altered vis-a- vis a native clostridial HN domain sequence. In one embodiment, the modification may involve one or more conservative amino acid substitutions. Other modifications may include removal or addition of one or more amino acid residues vis-a-vis a native clostridial HN sequence. However, any such fragment or variant must retain the aforementioned (i) translocation and/or (ii) improved solubility function." (pp. 6-7; see also p. 13).

The specification disclosed various construct variants (see pgs. 64-78). The specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity of the intact protein. Therefore the specification has not set

forth any enablement with regard to the myriad possibilities of the fragments or variants in each of the first, second, nor the myriad possible combinations of these fragments or variants of each of these domains that would comprise the single chain polypeptide as claimed. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed domains, for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species, which could not be distinguished without undue experimentation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions that would encompass the fragments and variants of the domains of the single chain polypeptide as presently claimed. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model.

State of the Art

It is known in the art that derivatives (i.e., fragments or variants), which are obtained by substitutions, deletions, or modifications of the amino acids of a protein alter the function of the protein. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three

dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306).

Houghten et al. teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al. teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24) and (see in its entirety Houghten et al., "Relative Importance of Position and Individual Amino Acid Residues in Peptide Antigen-Antibody Interactions: Implications in the Mechanism of Antigenic Drift and Antigenic Shift," Vaccines (1986) 86:21-25). It is not always possible to make the derivatives that retain immunodominant regions and immunological activity if the regions have been altered. For the reasons set forth supra, the state of the art has limitations to the single chain polypeptide structure comprising fragments or variants of the domains and further still be able maintain its function as claimed is unpredictable.

In conclusion, the claimed inventions are not enabled for a single chain polypeptide comprising fragments or variants thereof of the Clostridial neurotoxin light chain, or SEQ ID NO:66, nor a portion of Clostridial neurotoxin heavy chain. The claims encompassing all fragments and variants of clostridial neurotoxin light chain, clostridial neurotoxin heavy chain, and further fragments and variants of SEQ ID NO: 66 is overly broad. It is not routine in the art to screen for positions within the protein's sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility limited in any protein. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art. In view of the lack of support in the art and specification, associated with regard to the single chain polypeptide as claimed and the changes which can be made in the single chain polypeptide structure to make it a fragment or variant of the domains and still maintain their function as claimed, it would require

undue experimentation on the part of the skilled artisan to make and use the single chain polypeptide as claimed. Therefore the claims are not enabled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1, 2-3, 5, and 14, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to independent claim 1, the claim is vague and indefinite in the recitation of "capable of'. It has been held that the recitation that an element is "capable of' performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. In re Hutchison, 69 USPQ 138.

As to independent claim 1 and dependent claim 5, reciting the phrase "portion". However, neither the claim nor the specification clearly defines nor sets forth the meaning or means to assess "portion". "Portion" has no art defined meaning with respect to a polypeptide. Therefore, the skilled artisan would not be readily apprised of the metes and bounds of "portion" nor how to assess such. It is unclear how to interpret what is considered "portion" and it is an undefined segment and inasmuch as it is not a recognized term and not defined in the specification.

As to dependent claims 2-3, 5, and 14, reciting the limitation "clostridial toxin heavy chain", claim 1 recites a "clostridial neurotoxin light chain". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 1-18, 24, and 26-30 rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al. US Patent No. 7,192596 Date March 20, 2007 US Filing Date September 12, 2002.

The applied reference has a common inventor (Shone, Foster, Chaddock, Marks, Sutton, Stancombe, Wayne) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

15. Claims 1-3, 5-15, and 17-18 rejected under 35 U.S.C. 102(e) as being anticipated by Shone et al. US Application 20050244435 US Publication and Filing Date March 11, 2005.

The applied reference has a common inventor (Shone, Foster, Chaddock, Marks, Sutton, Stancombe, Wayne) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina Archie
Examiner
Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645